22. (New) A process as claimed in claim 18, wherein in b) Me or R(6) is the cation of an alkali metal salt or of a trialkylammonium salt.

I. Status of the claims

Claims 11-22 are pending in this application. The claims are largely re-written from earlier claims, now in clean form. Claims 11-14 are compound claims, claim 15 is a composition claim, claims 16-17 are method of use claims, and claims 18-22 are method of making claims. Claim 18 corresponds to previous claim 3, which was withdrawn from consideration as directed to non-elected subject matter. Claims 19-22 depend from claim 18. In the Office action dated June 16, 1998, the Examiner stated that process claims reciting compounds of the same scope as the allowed compounds would be rejoined for examination once the compound claims were found allowable.

This case was previously on appeal to the Board of Patent Appeals and Interferences. In light of the significant time delay in receiving a decision on appeal, applicants take this opportunity to restart prosecution and present additional arguments in favor of patentability of the claims.

II. Rejection of claims under 35 U.S.C. § 103(a)

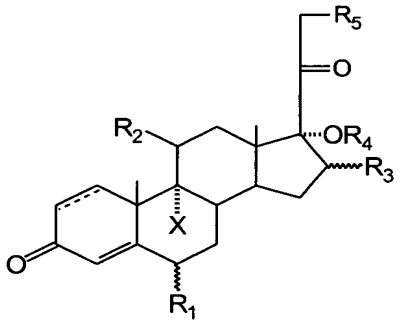
The Examiner rejected all previous claims as obvious under 35 U.S.C. § 103(a) over U.S. Patent No. 4,655,971 to Page et al. ("Page"). The Examiner stated that Page teaches 17, 21-dicarboxylic esters of 4-pregnen-3,20-diones having either an oxo or a hydroxy group in the 11-position. The Examiner further asserted that the Page compounds contained substituents "similar" to the instant claims in the 6, 9, and 16 positions, and that they may also contain a double bond in the 1 position. The Examiner also argued that Page teaches the use of the compounds in pharmaceutical compositions for the treatment of corticosteroid-responsive dermatosis.

The Examiner particularly emphasized Page's disclosure of betamethasone-17-valerate-21-acetate and betamethasone-17-benzoate in Examples 9 and 19. Conceding that those two compounds differ from the present compounds by having an

acetate or hydroxyl group in the 21-position, respectively, the Examiner nonetheless asserted that Page teaches an equivalence between a hydroxyl group and an acyl group in the 21-position, and an equivalence between acyl groups having an alkyl and an aralkyl moiety. The Examiner concluded that it would therefore have been obvious to modify the Page compounds to create an aralkyl acyl group in the 21-position.

A. The Examiner has not established a prima facie case of obviousness

Page discloses a process of preparing steroidal esters of the following formula:



where substituents R_1 to R_5 and X have the definitions set forth in Page. The R_5 substituent of Page corresponds generally to the portion of the side chain in the 21-position of the presently claimed compounds beginning with the oxygen that follows the CH_2 group. This portion of the claimed compound is -O-CO-[(C_1-C_4)-alkyl]-phenyl, with the phenyl being unsubstituted or substituted by the radicals recited in claim 11.

One skilled in the art would not have been motivated to make selections of substituents from Page to approximate the claimed invention. In order to have done so, and for the 21-position alone, one skilled in the art would have needed to define R_5 as R_6 (instead of as a hydroxyl group), define R_6 as OR_7 (instead of as a hydrogen or as one or two halogen atom substituents), where R_7 is an acyl group of the formula R'CO, and define R' as an aralkyl group of 7 to 8 carbon atoms (instead of a straight, branched, or cyclic alkyl group of 1 to 16 carbon atoms and instead of a phenyl group).

Nothing in Page or the prior art as a whole guides the selections above. Absent any such guidance, Page does not render the present invention obvious.

The obviousness issue here is analogous to that decided in In re Baird, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994). In Baird, the applicant claimed a flash fusible toner comprising a binder resin which was a bisphenol A polyester containing an aliphatic dicarboxylic acid selected from succinic acid, glutaric acid, and adipic acid. The Examiner rejected the claim as obvious over a patent to Knapp, which disclosed esterification of diphenol compounds and dicarboxylic acids. Recognizing that bisphenol A could have been derived when specific variables were chosen from the Knapp disclosure, the Examiner reasoned that the claimed compound "may be easily derived from the generic formula of the diphenol in Knapp and all the motivation the worker of ordinary skill in the art needs to arrive at the particular polyester of the instant claim is to follow that formula." Id. at 1551. This rejection was upheld by the Board, but the Federal Circuit reversed.

The Baird court first noted that "[t]he fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious." Id. at 1552. Instead, the prior art must suggest the compound. Id. at 1552. In light of this test for obviousness, the court noted that "[w]hile the Knapp formula unquestionably encompasses bisphenol A when specific variables are chosen, there is nothing in the disclosure of Knapp suggesting that one should select such variables." Id. Apart from the generic disclosure in Knapp, the court also noted that the 15 specific diphenol compounds disclosed in Knapp were more complex than bisphenol A, rendering the Knapp disclosure as actually teaching away from the bisphenol A compound claimed by the applicants. Id. ("Indeed, Knapp appears to teach away from the selection of bisphenol A by focusing on more complex diphenols."). The court therefore ultimately concluded that the applicants had claimed a compound that was not taught or suggested by Knapp.

The Examiner argues in the present case that In re Baird is not applicable to the pending claims, contending that the claims encompass numerous compounds, and the claim on appeal in Baird was directed only to a specific compound. Section 2144.08 of the MPEP, however, relies on In re Baird in formulating the examination procedures for determining the obviousness of either a single species *or a subgenus* of a prior art disclosure. The Examiner's interpretation of In re Baird as applicable only to claims directed to a single species compound is therefore at odds with the interpretation of In re Baird given by the Patent and Trademark Office, which uses the In re Baird analysis to subgenus as well as species claims. Applicants should therefore be entitled to rely on the reasoning of In re Baird for the pending claims.

B. One skilled in the art would not have been motivated to modify Examples 9 and 19 of Page as proposed by the Examiner

Aside from the generic disclosure, the specific compounds taught in Page likewise do not provide the motivation to make the claimed compounds. The Examiner particularly emphasized the compounds of Examples 9 and 19 of Page, but even conceded that the radicals at the 21-position of those compounds are hydroxyl or acetate groups, not -O-CO-[(C_1-C_4)-alkyl]-phenyl groups. In fact, each compound of Examples 1-28, the 10 specific compounds listed in Example 29, and the 5 compounds in Examples 30-34 all recite aliphatic group substituents in the 21-position, not -O-CO-[(C_1-C_4)-alkyl]-phenyl groups. Furthermore, and following the reasoning of In re Baird, Page's disclosure of these different specific compounds, which conspicuously lack the 21- position chain used by applicants, and do not contain any phenyl groups at all, actually teaches away from the present invention. See In re Baird, 29 U.S.P.Q.2d at 1552. See also MPEP § 2144.08 ("disclosure of dissimilar species can provide teaching away") (citing In re Baird).

Even if one skilled in the art would have desired to modify specific compounds in Page to derive new compounds, nothing in Page or in the art generally would have suggested starting with the compounds of Example 9 or 19 over any others. In this

regard, applicants bring to the Examiner's attention new evidence that would have counseled against using the compounds of Example 9 or 19 as starting points. Applicants attach relevant pages from of "Dermatika," Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, pp. 322-344 (1992), which discusses various properties of compounds, including betamethasone-17 benzoate and betamethasone 17-valerate. The discussion of betamethasone-17 benzoate begins on column 2 of page 332 of the document and, for stability of the compound, refers to the discussion of betamethasone-17 valerate in column 1 on page 333 (in translation "stability: see betamethasone 17-valerate"). Under the category betamethasone-17 valerate, the document states, in translation from the second column of page 334, last 20 lines, as follows:

> "Stability: The compound is unstable to light.
> Corticosteroid-17-monoester rearrange easily into 21-monoester in the presence of acids or bases. The 21-monoester of corticosteroids is generally significantly less pharmaceutically active than the respective 17-monoester. Betamethasone-21-valerate has only about 15% of the biological activity of the 17-valerate.
> This isomerization occurs particularly quickly in an alkaline milieu. Thus in ointments the 17-valerate is converted to 75% within 5 days under weakly alkaline pH values. Weakly acidic pH-values (for instance the addition of 0.005% phosphoric acid) are stabilizing. The isomerization catalyzed by acids starts significantly only with clearly lower pH- values.

In light of the above, the compounds of Examples 9 and 19 of Page would have been regarded as having poor stability. Assuming that there is an expectation of similar properties between structurally similar compounds, those skilled in the art would have been dissuaded from using the compounds of Examples 9 and 19 as starting points for deriving new compounds, as they would have expected such new compounds to have poor stability as well.

Even if one skilled in the art would have desired to modify the compounds of Example 9 and 19, the Examiner has not explained why that person would have chosen to specifically modify the R_5 substituent of those two particular Examples, in the specific

way suggested by the Examiner, while leaving all other substituents in such a way that they would approximate the corresponding substituents of the presently claimed compounds. The translated quotation above actually evidences that those skilled in the art would have regarded 21-esters as less active than 17-esters, which would actually dissuade one skilled in the art from selecting a 21-ester as is claimed.

The Examiner asserts that the motivation to derive applicants' compounds may be found in Page because it allegedly teaches an equivalence between a hydroxyl group and an acyl group in the 21-position, and an equivalence between acyl groups having an alkyl and an aralkyl moiety. The Examiner's assumptions about "equivalence" between the various substituents in the Page formula, however, appear to disregard the requirement that the art motivate the swap of substituents on the compounds. The mere theoretical possibility of selecting the compounds of Examples 9 and 19 of Page, and the theoretical possibility of modifying those compounds in the way suggested by the Examiner, by itself is insufficient. Instead, that assumption contradicts the reasoning of In re Baird. In that decision, the specific examples disclosed in the prior art could very well have been modified, using substituents that were disclosed as alternatives to each other in the prior art references, to arrive at the claimed compound. Even so, nothing in the generic disclosure and specific examples motivated those substitutions, rendering those disclosures insufficient to create the *prima facie* case of obviousness. Furthermore, as explained above, Page's emphasis on the dissimilar aliphatic 21-position substituents in all the disclosed examples, including Examples 9 and 19, actually acts as a teaching away from the present invention, not a teaching of equivalency.

Aside from Page itself, the prior art as a whole did not suggest the Examiner's proposed modification. For this purpose, applicants refer to the teachings of all patents cited by the Examiner in the Notice of Reference Cited that accompanied the Office action dated July 25, 1995 (Paper No. 7). None of the patents teaches the 21- position substitution used by applicants in the present claims. Two of the patents have an

effective filing date subsequent to Page, and one of those even names Philip R. Page as a co-inventor. As the propriety of the Examiner's proposed modifications is determined by the teachings of the prior art as a whole, these patents are relevant to show that the state of the art did not motivate those modifications.

U.S. Patent No. 5,026,693 to Villax et al., which names Philip R. Page as a co-inventor, teaches esters of 9α-fluoro and chloro-corticosteroids having a substituent Y that corresponds to applicants' side chain in the 21- position following the CH_2 group. Y of Villax et al. can be, *inter alia*, OR_1, where R_1 may be a benzoyl group (see col. 1, lines 64 and 65), but Y cannot be a group such as $C_6H_5CH_2$-CO- or $C_6H_5CH_2CH_2$-CO-. Therefore, Villax does not suggest compounds having -O-CO-[(C_1-C_4)-alkyl]-phenyl groups.

U.S. Patent No. 4,619,922 to Annen et al. teaches 6α,16α-dimethyl corticoids having a substituent Y that corresponds to applicants' side chain in the 21- position following the CH_2 group. The Y substituent of Annen et al. may be benzyloxy (see col. 1, lines 37-39) but there is no suggestion of compounds having -O-CO-[(C_1-C_4)-alkyl]-phenyl groups.

Having effective filing dates subsequent to Page, these patents confirm that one skilled in the art, even when in possession of the Page disclosure, would not have been motivated to make the present compounds.

Likewise, a number of patents that may have effective filing dates prior to Page also would not have suggested the Examiner's proposed modifications. U.S. Patent No. 4,918,065 to Stindl et al. teaches corticoids having a substituent Z that corresponds to applicants' side chain in the 21- position following the CH_2 group. The Z substituent of Stindl et al. may be benzyloxy (see col. 1, lines 58-59) but there is no suggestion of -O-CO-[(C_1-C_4)-alkyl]-phenyl groups. U.S. Patent No. 4,701,451 to Annen et al. teaches 6,16-dimethylcorticoids having a substituent Y that corresponds to applicants' side chain in the 21- position following the CH_2 group. The Y substituent of Annen et al. may

be benzyloxy (see col. 1, lines 40-41) but there is no suggestion of -O-CO-[(C_1-C_4)-alkyl]-phenyl groups.

U.S. Patent No. 4,645,763 to Annen et al. teaches 6α-methyl corticoids having a substituent X that corresponds to applicants' side chain in the 21- position following the CH_2 group. The X substituent of Annen et al. may be acyloxy (see col. 1, lines 27-28) or benzyloxy (col. 8, lines 53-54), but there is no suggestion of -O-CO-[(C_1-C_4)-alkyl]-phenyl groups. U.S. Patent No. 4,567,172 to Kamano et al. teaches 6α-methylprednisolone derivatives having a substituent -O-R^1, where R^1 may be -CO-R^3, and R^3 may be a phenyl group (see col. 2, lines 40-63). This disclosure does not suggest compounds having -O-CO-[(C_1-C_4)-alkyl]-phenyl groups. Finally, U.S. Patent No. 4,555,507 to Annen et al. teaches 6,16-dimethylcorticoids having a substituent Y that corresponds to applicants' side chain in the 21- position following the CH_2 group. The Y substituent of Annen et al. may be benzyloxy (see col. 1, lines 38-39) but there is no suggestion of -O-CO-[(C_1-C_4)-alkyl]-phenyl groups.

In light of the above, the prior art as a whole would not have motivated one skilled in the art to make the claimed compounds. Absent a *prima facie* showing of obviousness, this rejection should be withdrawn.

C. Claims 13 and 14 are each patentable over Page

Claims 13, and 14 depend from claim 11 and further define the substituents A, Y, Z, (C_1-C_4)-alkyl, R(1), R(2), and R(3) in the formula I. As with the compounds of the formula I, the Page disclosure would not have motivated one skilled in the art to derive either of these two more specific compounds.

With respect to claim 13, nothing in Page would have suggested the simultaneous selection of the following substituents:

X as hydrogen (instead of chlorine or fluorine);

R_1 as hydrogen (instead of fluorine, chlorine or α- or β- methyl);

R_2 as hydroxyl (instead of halogen or oxo);

R_3 as hydrogen (instead of α- or β- methyl);

R_4 as an acyl group of the formula RCO, in which R is an aralkyl group of 7 to 8 carbon atoms (instead of R being an alkyl group containing 1 to 16 straight chained, branched, or cyclic carbon atoms and instead of a phenyl group);

R_5 as R_6 (instead of as a hydroxyl group),

R_6 as OR_7 (instead of as a hydrogen or as one or two halogen atom substituents),

R_7 as an acyl group of the formula R'CO, with R' as an aralkyl group of 7 to 8 carbon atoms (instead of R' as a straight, branched, or cyclic alkyl group of 1 to 16 carbon atoms and instead of a phenyl group), and

aralkyl group as a C_1-alkyl connected to unsubstituted phenyl.

Furthermore, one skilled in the art would not have been motivated to derive this compound in light of the compounds of Examples 9 or 19 of Page. More particularly, with respect to Example 9, Page did not suggest using hydrogen in place of fluorine in the variable X; replacing the methyl with a hydrogen in R_3; replacing the 17-valerate with -O-CO-phenyl; and replacing the 21-acetate with -O-CO-[C_1-alkyl]-phenyl. For Example 19, Page did not suggest swapping hydrogen in place of fluorine in the variable X; replacing the methyl with a hydrogen in R_3; or replacing the 21- hydroxyl with -O-CO-[C_1-alkyl]-phenyl.

With respect to claim 14, nothing in Page suggested the simultaneous selection of the following substituents:

X as fluorine (instead of hydrogen or chlorine);

R_1 as hydrogen (instead of fluorine, chlorine or α- or β- methyl);

R_2 as hydroxyl (instead of halogen or oxo);

R_3 as β-methyl (instead of hydrogen or α-methyl);

R_4 as an acyl group of the formula RCO, in which R is an aralkyl group of 7 to 8 carbon atoms (instead of R being an alkyl group containing 1 to 16 straight chained, branched, or cyclic carbon atoms and instead of a phenyl group);

R_5 as R_6 (instead of as a hydroxyl group),

R_6 as OR_7 (instead of as a hydrogen or as one or two halogen atom substituents),

R_7 as an acyl group of the formula R'CO, with R' as an aralkyl group of 7 to 8 carbon atoms (instead of R' as a straight, branched, or cyclic alkyl group of 1 to 16 carbon atoms and instead of a phenyl group), and

aralkyl group as a C_1-alkyl connected to unsubstituted phenyl.

Furthermore, one skilled in the art would not have been motivated to derive this compound in light of the compounds of Examples 9 or 19 of Page. More particularly, with respect to Example 9, Page did not suggest replacing the 17-valerate with -O-CO-phenyl; and replacing the 21-acetate with -O-CO-[C_1-alkyl]-phenyl. For Example 19, Page did not suggest replacing the 21- hydroxyl with -O-CO-[C_1-alkyl]-phenyl.

The rejection as it applies to claims 13 and 14 should be withdrawn.

D. The Unexpectedly superior properties of the claimed compounds would rebut any prima facie showing of obviousness

Even if the Examiner had established a *prima facie* case of obviousness, the claimed compounds possess unexpectedly better properties over the prior art that would rebut any such *prima facie* showing. Compounds having a 21-aryl ester or 21-hetaryl ester, as claimed, "often exhibit qualities of effect which are clearly superior, as regards the local/systemic ratio of antiinflammatory effect, to those of structurally related corticoid 17,21-dicarboxylic esters or structurally related corticoid 17-alkyl carbonate 21-carboxylic esters which do not carry any aryl or hetaryl group in the 21-acid residue."

Specification at page 5, lines 20-29. The compounds not having any aryl or hetaryl group in the 21-position obviously include compounds of Examples 9 and 19 of Page. Moreover, the claimed compounds "surprisingly" exhibit "a very good ratio of local to systemic antiinflammatory effect, which ratio is often markedly superior . . . to that of known corticoid 17-alkyl carbonate 21-esters, which do not carry any aryl or hetaryl group in the 21-ester radical, such as, for example, 21-ester groups having a 21-alkyl group." Specification at page 13, lines 20-30. Detailed pharmacological testing in support of these statements appears in the specification at page 15, line 12 to page 19, line 16.

These markedly superior and surprising properties of the claimed compounds constitute part of the invention "as a whole," that would rebut any *prima facie* case, if one had been established. As noted by the Federal Circuit, the properties of claimed compounds compared to prior art compounds must be given weight in analyzing the obviousness of the invention as a whole: "[c]learly, in determining patentability the Board was obligated to consider all the evidence of the properties of the claimed invention as a whole, compared with those of the prior art." In re Dillon, 16 U.S.P.Q.2d 1897, 1902 (Fed. Cir. 1990), decided *in banc*. Applicants also remind the Examiner that the obviousness determination must be considered all over again in light of these unexpected properties, as opposed to simply determining whether the asserted properties outweigh any pre-conceived conclusion of obviousness. See MPEP § 2144.08 ("A determination under 35 U.S.C. 103 should rest on all the evidence and should not be influenced by any earlier conclusion. . . . Thus, once the applicant has presented rebuttal evidence, Office personnel should reconsider any initial obviousness determination in view of the entire record.").

Conclusion

For the reasons given above, the Examiner has not established a *prima facie* case of obviousness. Even if such a *prima facie* case could have been established, the unexpectedly superior properties of the claimed compound over those of the prior art would rebut such a case. Applicants therefore respectfully request that the Examiner withdraw the rejection.

If there is any fee due in connection with the filing of this Preliminary Amendment, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

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